from the group consisting of αPKC and ZO-1.

12. (New) The method of claim 10, wherein said TJ leakiness is correlated with reduced phosphorylation state of occludin.

REMARKS

Claims 1-4 are currently pending in the present application.

Claims 1 and 2 have been canceled by the present amendment.

Claim 3 has been amended by the present amendment.

New claims 5-12 have been added by the present amendment.

Claim 3 has been amended to specify that the precancerous condition to be detected by the method is a precancerous lesion to the esophageal mucosa in a patient who is not experiencing ulcerative damage or bleeding from the gastrointestinal tract. Additionally, the step of measuring the level of at least one signature carbohydrate in the urine from said patient relative to urine levels observed from a control urine sample has also been inserted into the claim. Support for the foregoing amendments can be found on page 5, lines 1-7; page 14, lines 12-14; and page 14, lines 17-33.

New claim 5 is directed to detection of Barrett's condition, a precancerous condition of the esophagus. Support for this amendment can be found on page 5, lines 31-32 and page 14, lines 10-14.

New claim 6 specifies that the urine sample is

collected overnight following administration of said at least one signature carbohydrate. Support for this amendment is found at page 14, line 19.

New claim 7 depends from amended claim 3 and further comprises the steps of examining tight junction (TJ) leakiness in a tissue sample from the esophageal mucosa of the patient. Support of the amendment can be found on page 15, lines 1-14.

New claim 8 depends from new claim 7 and further specifies that the TJ leakiness is correlated with altered expression levels of a protein selected from the group consisting of αPKC and ZO-1. Support for this amendment can be found on page 10, lines 24-27 and page 11, lines 2-6.

New claim 9 depends from new claim 7 and further specifies that the TJ leakiness is correlated with reduced phosphorylation state of occludin. Support for this amendment can be found on page 11, lines 8-10.

New independent claim 10 is directed to methods of diagnosing Barrett's esophageal conditions by assaying urine sucrose levels in urine relative to a control urine sample coupled with examining TJ leakiness of tissue samples from the esophageal mucosa. Support for this amendment can be found on page 5, lines 1-7; page 5, lines 31-32; page 14, lines 10-33; and page 15, lines 1-14.

New claim 11 depends from new claim 10 and further specifies that the TJ leakiness is correlated with altered expression levels of a protein selected from the group consisting of αPKC and ZO-1. Support for this amendment can be found on page 10, lines 24-27 and page 11, lines 2-6.

New claim 12 depends from new claim 10 and further specifies that the TJ leakiness is correlated with reduced

phosphorylation state of occludin. Support for this amendment can be found on page 11, lines 8-10.

No new matter has been added by the foregoing amendments.

TRAVERSAL AND REQUEST FOR RECONSIDERATION OF REQUIREMENT FOR RESTRICTION

A restriction requirement under 35 U.S.C. §121 was set forth in the Official Action dated May 21, 2002 in the above-identified patent application. It is the Examiner's position that claims 1-4 in the present application are drawn to four (4) patentably distinct invention which are as follows:

Group I, claims 1-2 are drawn to diagnosing a precancerous condition comprising detecting a protein classified in Class 435, subclass 4, 7.1, 7.4.

Group II, claims 1-2 are drawn to diagnosing a cancerous condition comprising detecting a protein classified in class 435, subclass 4, 7.1, 7.4.

Group III, claims 3-4 are drawn to diagnosing a precancerous condition comprising detecting a carbohydrate classified in Class 435, subclass 4, 7.1, 7.4.

Group IV, claims 3-4 are drawn to diagnosing a cancerous condition comprising detecting a carbohydrate classified in Class 435, subclass 4, 7.1, 7.4.

Furthermore, at page 3 of the Official Action, the Examiner indicates that Groups I and II are further subject to

election of a single disclosed species, namely, a single or a combination of proteins trefoil factor, pepsin, and salivary amylase. At page 3 of the Official Action, the Examiner indicates that Groups III and IV are further subject to election of a single disclosed species, namely, a single or a combination of carbohydrates, mannitol and sucrose. At page 4 of the Official Action, the Examiner indicated that Groups I and III are further subject to election of a method of assay, namely, enzymatic assay or immunoassay.

The Examiner's attention is directed to the foregoing amendment, wherein claims 1 and 2 have been canceled. Therefore, the restriction requirement relating to Groups I and II have been rendered moot. In addition, Applicants respectfully maintain that the restriction requirement set forth above is improper for failing to comply with the relevant provisions of the Manual of Patent Examination Procedures (M.P.E.P.).

Specifically, it is the Examiner's position that a restriction is required between the species carbohydrates, namely, sucrose and mannitol, recited in claim 3, because they have different structures and functions. This restriction is respectfully traversed for the reasons set below. In fact, the two species, mannitol and sucrose, share similar structure, i.e., they are both carbohydrates, and they share similar properties, i.e., increased urine levels of which are associated with TJ leakiness in the esophageal mucosa. Moreover, the species carbohydrates are members of a Markush group. It is stated in MPEP §803.2 that:

> If the numbers of Markush group are sufficiently **few in number or so closely related** that a search and examination of the entire claim can be made **without serious**

> **burden**, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. (*emphasis added*)

In the instant case, a small number of carbohydrates (i.e., 2) are recited in the Markush group. Inasmuch as it would not pose a serious burden upon the Examiner to examine the signature carbohydrates in one group, it is improper to require Applicants to elect a single species for examination purposes.

The Examiner also asserts that claim 3 is a generic to a plurality of disclosed patentably distinct species comprising assay methods wherein the methods are materially distinct methods, namely, enzymatic assay and immunoassay. Again, this restriction requirement is respectfully traversed. As amended, claim 3 is directed to a method of detecting precancerous conditions by measuring increased urine levels of sucrose in a patient who has ingested an appropriate amount of at least one signature carbohydrate relative to control urine samples. It is well appreciated by those skilled in the art that the crux of the invention is directed to the discovery of correlation between increased urine levels of signature carbohydrates and precancerous or cancerous conditions of esophageal mucosa in a patient. It would also be appreciated by the skilled artisan that any assay method, including but not limited to chemical assay, enzymatic assay, and immunoassay, may be used in measuring urine levels of a signature carbohydrate. Thus, the use of different assay readout methodology, such as enzymatic assay and/or immunoassay, in measuring urine levels of signature carbohydrates does not affect the novelty or patentability of the claimed invention and does not make the species patentably

distinct. Therefore, Applicants respectfully assert that it is improper to draw restriction between the readout methods for measuring the presence of signature carbohydrates.

In light of the foregoing remarks, the restriction requirement of May 21, 2002 should be withdrawn or at the very least modified.

In order to be fully responsive to the above-mentioned requirement, Applicants hereby elect, with traverse, the subject matter of Group III for consideration in this application, which includes claims amended claims 3 and 4 and newly added claims 5-8, drawn to diagnosing a precancerous condition comprising detecting a carbohydrate. Applicants also elect, with traverse, sucrose as the species of carbohydrate to be examined. Applicants additionally elect, with traverse, the use of enzymatic assays to detect sucrose levels in the presently claimed methods.

Applicants reserve the right to file one or more continuing applications, as provided in 35 U.S.C. §121, on the subject matter of any claims finally held withdrawn from consideration in this application.

Early and favorable action on the merits of this application is respectfully solicited.

Respectfully submitted,
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MARKED UP DRAFT OF AMENDED CLAIMS

Please amend claim 3 as follows:

3. (Amended) A method of diagnosing a precancerous [or cancerous]condition[s] of esophageal mucosa in a [mammal]patient comprising [obtaining a biological sample from a gastrointestinal site of said mammal and placing the sample into an enzymatic or immunologic assay to detect the presence of a backleak of at least one signature carbohydrate in the gastrointestinal tract]the steps of:

a) administering to said patient an appropriate amount of at least one signature carbohydrate, said patient not having ulcerative disease of the gastrointestinal (GI) trat nor bleeding therefrom;

b) collecting urine voided by said patient during a suitable time period after the administration of said at least one signature carbohydrate;

c) measuring levels of said at least one signature carbohydrate present in the urine collected in step b); and

d) comparing the urine levels of said at least one signature carbohydrate in said patient with a control urine sample, wherein an increase in the urine levels of said at least one carbohydrate in said patient is indicative of the precancerous condition of esophageal mucosa in said patient.

Please add new claims 5-12 as follows:

5. (New) The method of claim 3, wherein said precancerous condition of esophageal mucosa is Barrett's esophageal condition.

6. (New) The method of claim 3, wherein said urine is collected overnight following the administration of said signature carbohydrate.

7. (New) The method of claim 3, further comprising the steps of:

e) obtaining a tissue sample from the esophageal mucosa of said patient;

f) examining tight junction (TJ) leakiness of said tissue sample; and

g) comparing the TJ leakiness of said tissue sample from said patient with that from a control tissue sample, wherein an increase in the TJ leakiness of said tissue sample from said patient is indicative of the precancerous condition of esophageal

mucosa in said patient.

8. (New) The method of claim 7, wherein said TJ leakiness is correlated with altered expression levels of a protein selected from the group consisting of αPKC and ZO-1.

9. (New) The method of claim 7, wherein said TJ leakiness is correlated with reduced phosphorylation state of occludin.

10. (New) (Amended) A method of diagnosing Barrett's esophageal condition in a patient comprising the steps of:

a) administering to said patient an appropriate amount of sucrose, said patient not having ulcerative disease of the GI tract nor bleeding therefrom;

b) collecting urine voided by said patient during a suitable time period after the administration of sucrose;

c) measuring levels of sucrose present in the urine collected in step b); and

d) comparing the urine levels of sucrose in said patient with a control urine sample, wherein an increase in the urine levels of sucrose in said patient is indicative of the Barrett's esophageal condition;

e) obtaining a tissue sample from the esophageal mucosa of said patient;

f) examining tight junction (TJ) leakiness of said tissue sample; and

g) comparing the TJ leakiness of said tissue sample from said patient with that from a control tissue sample, wherein an increase in the TJ leakiness of said tissue sample from said patient is indicative of the Barrett's esophageal condition in said patient.

11. (New) The method of claim 10, wherein said TJ leakiness is correlated with altered expression levels a protein selected from the group consisting of αPKC and ZO-1.

12. (New) The method of claim 10, wherein said TJ leakiness is correlated with reduced phosphorylation state of occludin.

CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS

3. (Amended) A method of diagnosing a precancerous condition of esophageal mucosa in a patient comprising the steps of:

a) administering to said patient an appropriate amount of at least one signature carbohydrate, said patient not having ulcerative disease of the gastrointestinal (GI) trat nor bleeding therefrom;

b) collecting urine voided by said patient during a suitable time period after the administration of said at least one signature carbohydrate;

c) measuring levels of said at least one signature carbohydrate present in the urine collected in step b); and

d) comparing the urine levels of said at least one signature carbohydrate in said patient with a control urine sample, wherein an increase in the urine levels of said at least one carbohydrate in said patient is indicative of the precancerous condition of esophageal mucosa in said patient.

4. The method of claim 3, wherein said signature carbohydrate is at least one of the group of mannitol and sucrose.

5. (New) The method of claim 3, wherein said precancerous condition of esophageal mucosa is Barrett's esophageal condition.

6. (New) The method of claim 3, wherein said urine is collected overnight following the administration of said signature carbohydrate.

7. (New) The method of claim 3, further comprising the steps of:

e) obtaining a tissue sample from the esophageal mucosa of said patient;

f) examining tight junction (TJ) leakiness of said tissue sample; and

g) comparing the TJ leakiness of said tissue sample from said patient with that from a control tissue sample, wherein an increase in the TJ leakiness of said tissue sample from said patient is indicative of the precancerous condition of esophageal mucosa in said patient.

8. (New) The method of claim 7, wherein said TJ leakiness

is correlated with altered expression levels of a protein selected from the group consisting of αPKC and ZO-1.

9. (New) The method of claim 7, wherein said TJ leakiness is correlated with reduced phosphorylation state of occludin.

10. (New) (Amended) A method of diagnosing Barrett's esophageal condition in a patient comprising the steps of:

a) administering to said patient an appropriate amount of sucrose, said patient not having ulcerative disease of the GI tract nor bleeding therefrom;

b) collecting urine voided by said patient during a suitable time period after the administration of sucrose;

c) measuring levels of sucrose present in the urine collected in step b); and

d) comparing the urine levels of sucrose in said patient with a control urine sample, wherein an increase in the urine levels of sucrose in said patient is indicative of the Barrett's esophageal condition;

e) obtaining a tissue sample from the esophageal mucosa of said patient;

f) examining tight junction (TJ) leakiness of said tissue sample; and

g) comparing the TJ leakiness of said tissue sample from said patient with that from a control tissue sample, wherein an increase in the TJ leakiness of said tissue sample from said patient is indicative of the Barrett's esophageal condition in said patient.

11. (New) The method of claim 10, wherein said TJ leakiness is correlated with altered expression levels a protein selected from the group consisting of αPKC and ZO-1.

12. (New) The method of claim 10, wherein said TJ leakiness is correlated with reduced phosphorylation state of occludin.